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CASE REPORT

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Inappropriate prescription of corticosteroid therapy during inflammatory ileo-colitis revealing disseminated tuberculosis with digestive involvement: Two case reports

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Abstract

It is essential to differentiate intestinal tuberculosis from Crohn's disease because of the therapeutic implications of Crohn's disease, which can exacerbate the symptoms of tuberculosis.

KEYWORDS

Crohn's disease, gastrointestinal tuberculosis, immunosuppressive, Madagascar

1 | INTRODUCTION

The similarity between intestinal tuberculosis (ITB) and Crohn's disease (CD) could lead us to erroneously prescribe corticosteroid therapy. Therefore, it is essential to differentiate the two pathologies because of the therapeutic implications of CD, which can exacerbate the symptoms of tuberculosis (TB).

Intestinal tuberculosis and CD are similar chronic granulomatous diseases making a real diagnostic problem.[1,2] Gastrointestinal tuberculosis is responsible for significant morbidity and mortality but can be cured with anti-tuberculosis chemotherapy for 6 months. Its frequency is estimated at 3%-5%.[2,3] Crohn's disease is a chronic disease that progresses over time and requires lifelong treatment to maintain remission. It has a high prevalence in industrialized countries but rare in Africa, especially in Sub-Saharan Africa.[3,4] It is notoriously difficult to differentiate ITB from CD, due to the similarity between the two pathologies from a clinical, radiological, endoscopic, and even histopathological

point of view.[1,3] Confusion between these two diseases can lead us to erroneously prescribe corticosteroid therapy. This can worsen the symptoms of TB and promote the development of complications.[5-7] The elimination of ITB before the initiation of immunosuppressive therapy remains fundamental in the event of inflammatory ileo-colitis. Our objective is to report two cases of disseminated TB with digestive involvement revealed following corticosteroid therapy in order to alert our colleagues in endemic areas to the dangerousness of initiating corticosteroid therapy without formally ruling out ITB.

2 | CASE REPORT

2.1 | CASE 1

A 31-year-old woman, accountant was followed up for an outpatient for abdominal pain and altered general condition. The patient had been vaccinated against TB in childhood according to the expanded immunization program. She had neither previous history of TB nor notion of TB contagion in her entourage. Since May 2017, the patient presented a febrile diarrhea, abdominal pain, and weight loss. Physical examination showed a defense in the right lumbar and iliac region. The proctological examination was normal. We had not objectified extra-digestive signs (cutaneous, articular, ocular, and biliary). The abdominal and pelvic ultrasound on 06/08/17 was normal. The ileocolonoscopy of 06/12/17 showed the presence of deepening circumferential ulcerations of the right colon and of the low cecal fundus with modification of the ileocecal valves. The terminal ileum was normal. The histology of the colonic biopsies of 06/23/17 revealed focal ulcerations with a discreet architectural modification, a small focus of basal plasmacytosis, without inflammatory granuloma, without caseous necrosis and without Ziehl stain micro-sticks. Despite the absence of granuloma, the morphological signs of the biopsies could be in favor of CD. The first chest X-ray on 07/05/17 was normal. The first test for acid-fast bacilli (AFB) in sputum was negative on 07/10/17. All the symptoms suggested severe ileocecal CD. Corticosteroid therapy (Solupred®) at a dose of 1 mg/kg/day was started on 07/17/17. The patient was hospitalized on 08/11/17 (1 month from Solupred®) for respiratory distress and increased digestive symptoms. The corticosteroid therapy was immediately stopped. The general examination reported hemodynamic instability with a hypotension (70/40 mm Hg), tachycardia(130/mm), tachypnea(31/mm), oxygen desaturation at 88% in ambient air, and fever at 39.8°C signifying severe sepsis. Clinical examination reported bilateral pulmonary crackling rales and diffuse abdominal defense. The management of severe sepsis was immediately initiated with filling with physiological serum combined with a double antibiotic therapy such as 3rd generation cephalosporin (Ceftriaxone) and aminoglycoside (Gentamicin). The second chest X-ray of 08/11/17 revealed diffuse bilateral alveolar opacities (Figure 1). The chest CT scan of 08/11/17 showed diffuse heterogeneous infiltrates (Figure 2A) with a 50 mm cavitary lesion of the apex of the right lung (Figure 2B) suggesting TB. The abdominal and pelvic CT scan of 08/11/17 was normal. Laboratory investigations of 08/11/17 showed a clear inflammatory syndrome with a C-reactive Protein (CRP) at 186 mg/L (Table 1). The second search for acid-alcohol-resistant bacilli in the sputum on 08/14/17 came back positive on direct examination. Severe sepsis in the context of disseminated TB with digestive involvement has been suggested. Anti-tuberculosis therapy according to the national protocol was initiated on 08/14/17. The digestive and respiratory outcomes were satisfying, with appetite resuming after 1 week of treatment. Apyrexia was only demonstrated from the 17th day (08/31/17) of the anti-tuberculosis therapy. The diagnosis of disseminated TB with digestive involvement was based on clinical, biological, radiological, and endoscopic arguments associated with a satisfying response to anti-tuberculosis treatment. The reassessment of 10/15/2017 reported an absence of clinico-radiological TB signs and a return to normal weight. The patient had been declared cured at the end of the treatment.

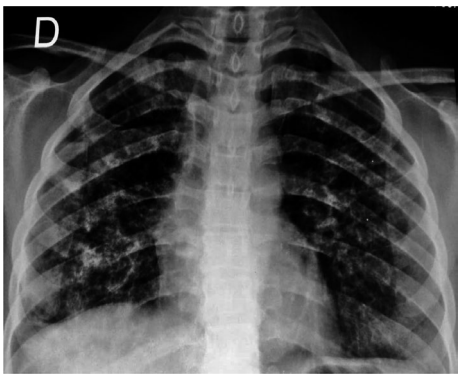

FIGURE 1 Chest X-ray in 31-year-old woman (Case 1) shows diffuse bilateral alveolar opacities

2.2 | CASE 2

A 51-year-old woman had since December 2020 intermittent episodes of rectal bleeding alternating with febrile diarrhea with a weight loss of 15 kg in 2 months requiring her first hospitalization (01/15/20). The patient did not report any history of TB or any notion of TB contagion in her entourage. Initial clinical examination reported mucocutaneous pallor and diffuse abdominal pain. The patient did not present extra-digestive symptoms. Laboratory investigations

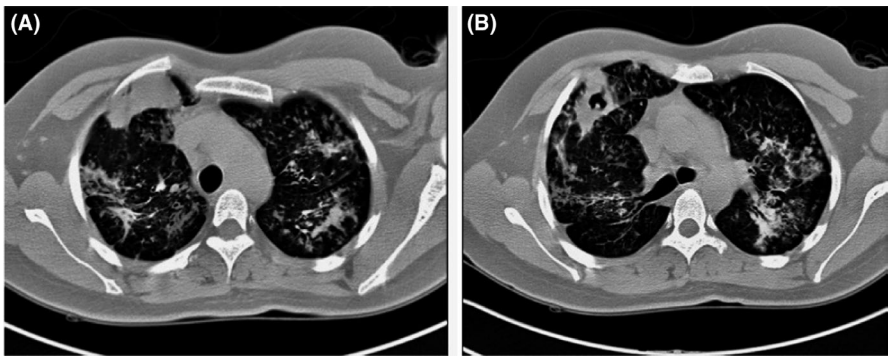

FIGURE 2 A, B: Chest CT scan in 31-year-old woman (Case 1) shows diffuse heterogeneous infiltrates A, with a 50 mm cavitary lesion of the apex of the right lung B

TABLE 1 Laboratory tests of our patients upon admission and readmission

			Case 2	
Biology tests	**Cutoff values**	**Case 1 (11.08.17)**	**First admission (01/15/2020)**	**Readmission (03/05/20)**
Hemoglobin (g/L)	110-160	116	107	66
MCV (fL)	80-95	8070	877	86
Leukocytes (G/L)	3.8-11	1022	2280	2440
PNN (G/L)	2.0-7.5	7154	19 836	20 984
Lymphocytes (G/L)	1-4.8	1298	2280	2440
Platelets (G/L)	150-450	441	524	289
PL /CTA ratio	75%-100%/0.80-1.20	100%/0.90	95%/0.86	86%/0.79
Creatinine (µmol/L)	44-105	67	75	54
Ferritin (ng/mL)	4.63-204	15	120	72
Total Protidemia (g/L)	64-83	77	54	46
Albuminemia (g/L)	35-53	4050	31	26
AST (U/L)	<35	11	10	163
ALT (U/L)	<45	5	163	100
CRP (mg/L)	<10	186	108	265
HIV	—	Negative	Negative	—
Stool culture	—	Negative	Negative	—
Parasitological test of stool	—	Negative	Negative	—
Calprotectin (mg/kg)	<50	493	—	—

Abbreviations: ALT, alanine amino-transferase; AST, aspartate amino-transferase; CRP, C-reactive Protein; CTA, cephalin time activated; HIV, human immunodeficiency virus; MCV, mean corpuscular volume; PL, prothrombin Level; PNN, polynuclear neutrophil.

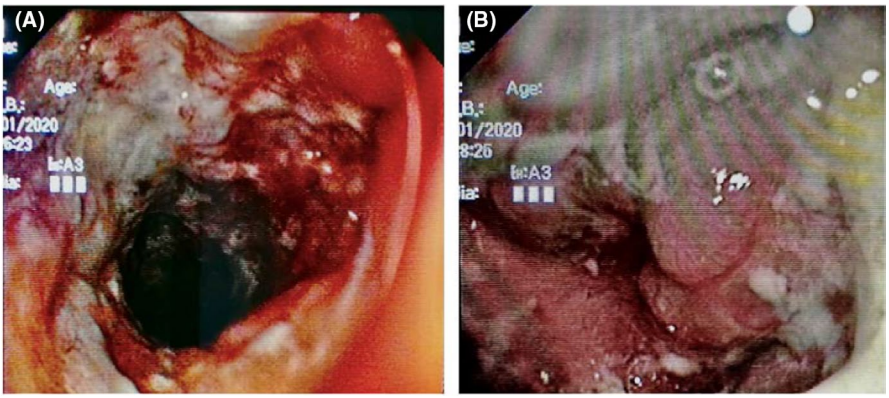

FIGURE 3 A, B: Coloscopy in 51-year-old woman (Case 2) shows circumferential ulcerations and sometimes deep of the rectum A, and inflammatory stenosis at 20 cm from the anal margin B

on 01/15/20 showed a significant inflammatory syndrome with a CRP at 186 mg/L associated with hyperleukocytosis at 22 800/mm^3 and anemia at 10.7 g/dL (Table 1). The upper gastrointestinal endoscopy on 01/16/20 was normal. The abdominal and pelvic CT scan of 01/16/20 revealed a thickening of the left colon. The ileo-colonoscopy of 01/23/20 revealed circumferential ulcerations and sometimes deep of the rectum (Figure 3A). Progression stopped at 20 cm from the anal margin because of an inflammatory stenosis (Figure 3B). The histology of the rectal biopsies on 02/01/20 showed samples consisting of edematous fibrous tissue, densely infiltrated by lymphocytes and polynuclear neutrophils and surrounded by fibrino-leukocyte coatings, without epithelioid granuloma, lymphocytic follicular hyperplasia, plasma cell infiltrate, caseous necrosis, and micro-sticks in Ziehl's stain. Deep ulceration points to CD, but remains insufficient to make a diagnosis. The absence of plasma cell infiltrate does not allow referral to ulcerative colitis. A collegial decision opted to immediately start corticosteroid therapy (Prednisolone®) and bi-antibiotic therapy (3rd generation cephalosporin + Imidazole) in the context of severe acute colitis on 02/06/20. The patient had opted for discharge against medical advice on 02/10/20. The evolution was marked by an increase in digestive, septic, and respiratory manifestations with persistence of a gastrointestinal bleeding type melena with severe anemia poorly tolerated after 3 weeks of treatment, motivating a readmission with immediate stopping of corticosteroids on 03/04/20. General examination showed sepsis with hypotension (90/50 mm Hg), tachycardia (110/min), tachypnea (29/min), oxygen desaturation at 91%, and fever at 38.5°C. Physical examination reported bilateral alveolar condensation syndrome and diffuse abdominal defense. Laboratory investigations on 03/05/20 reported severe anemia at 6.6 g/dL hemoglobin and an increased in inflammatory syndrome with CRP at 265 mg/L and hyperleukocytosis at 24 400/mm^3 (Table 1). The chest X-ray showed bilateral and diffuse interstitial miliary images with some left upper lobe infiltrates suggestive of TB (Figure 4). The test for acid-fast bacilli was negative on direct examination. A second research was positive on GeneXpert®. The diagnosis of disseminated TB with digestive involvement has been suggested. Anti-tuberculosis therapy according to the national protocol was initiated immediately on 03/09/20. The rectosigmoidoscopy of 04/06/20 showed a clear improvement of the initial lesions with persistence of small ulcerations. The reassessment on 05/14/20 was satisfying with disappearance of digestive, respiratory, and infectious manifestations with a return to his normal weight. The patient had been declared cured at the end of treatment. The diagnosis of disseminated TB with digestive involvement was based on clinical, biological, radiological, and endoscopic arguments associated with a satisfying response to anti-tuberculosis treatment.

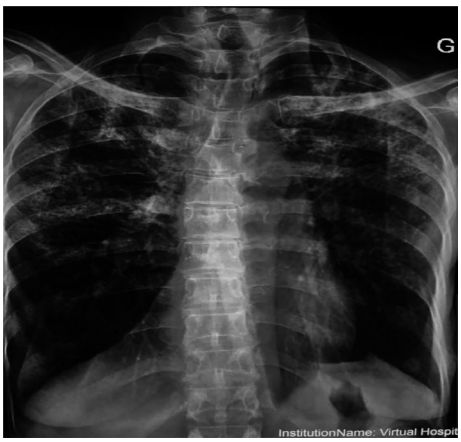

FIGURE 4 Chest X-ray in 51-year-old woman (Case 2) shows bilateral and diffuse interstitial miliary images with some left upper lobe infiltrates

3 | DISCUSSION

We report two observations of disseminated TB with digestive damage revealed by an inappropriate prescription of corticosteroid therapy in the context of inflammatory ileocolitis. In Madagascar, it is still difficult to differentiate ITB from CD due to the lack of technical facilities and insufficient resources of patients. We retain that ITB should be systematically mentioned first in endemic countries in the event of inflammatory ileo-colitis. Prescribing immunosuppressant is dangerous in this situation, and should only be prescribed after formal elimination of TB.

Intestinal tuberculosis is an extra-pulmonary form of TB, secondary to hematogenous dissemination, or by local extension following peritoneal involvement or endogenously from swallowed bacilliferous sputum in patients with active pulmonary forms.[1,8,9] Its frequency is estimated at 3%-5%.[1,2] Abdominal TB mainly affects young adults with a peak frequency between 21 and 45 years. The predominance of women has been observed in countries endemic to TB. Tuberculosis involvement mainly concerns the ileum, the ileocecal junction and then the colon.[1,8-10] CD remains a very rare disease in Africa, especially in sub-Saharan Africa.[3,4] In order of frequency, ITB should be mentioned before CD in an endemic TB zone in the event of inflammatory ileo-colitis.[3] Confusion between ITB and CD poses a real diagnostic problem and a very high diagnostic error rate ranging from 50% to 70%, causing inadequate prescription of corticosteroid therapy. This similarity concerns all aspects of these diseases, clinico-radiological, endoscopic, and even histopathological.[1-3] Clinical, radiological, and endoscopic criteria have been established by certain authors but they are disappointing.[1,3] The presence of ascites remains more frequent in the course of TB and has been judged as a more specific clinical criterion in favor of the latter.[11] Endoscopic differentiation

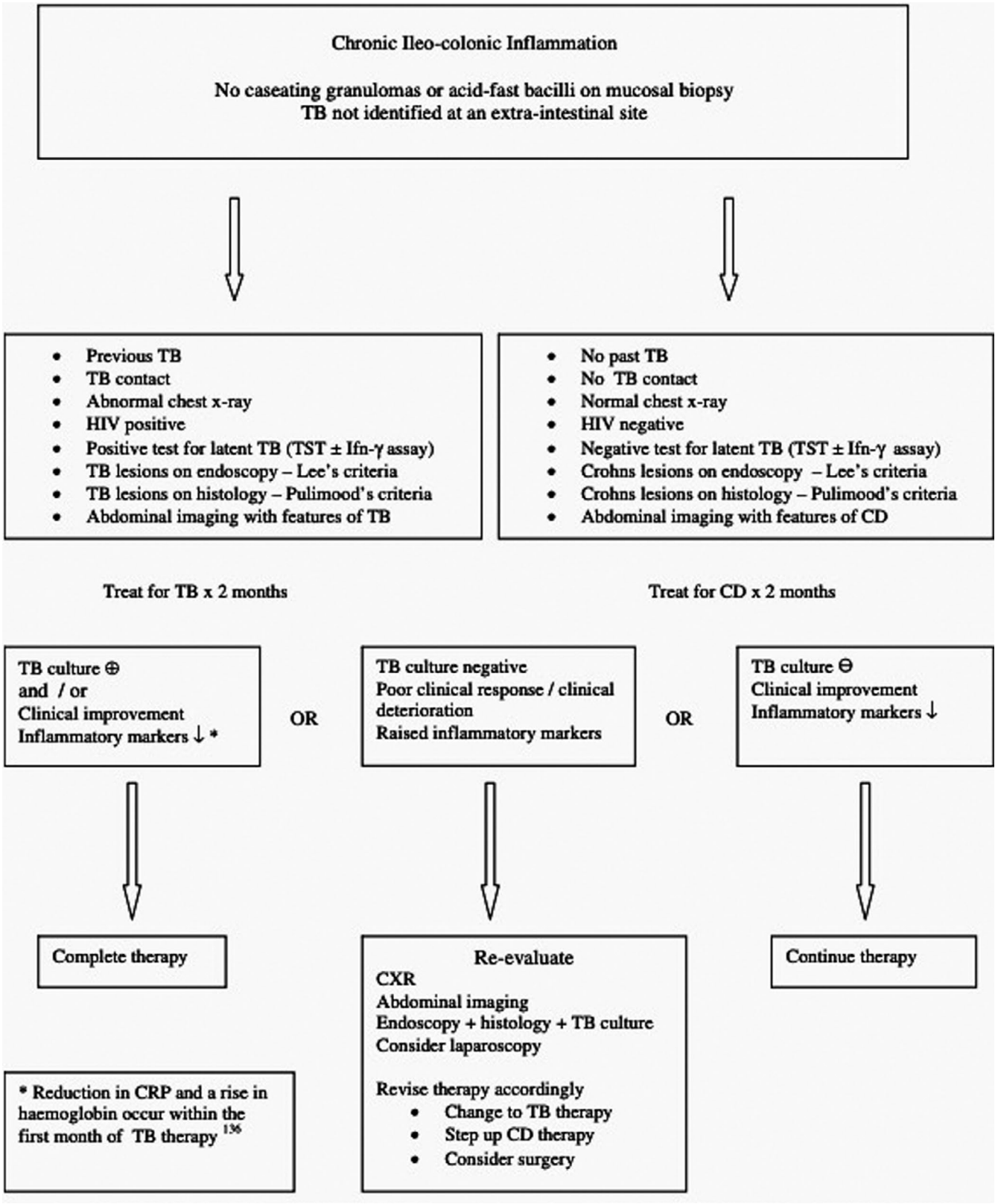

FIGURE 5 Treatment algorithm—Intestinal tuberculosis vs Crohn's Disease. Epstein D, Watermeyer G, Kirsch R. Review article: the diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. *AlimentPharmacol Ther*. 2007; 25:1373-88

in colonoscopy between ITB and CD is difficult since both diseases can present with mucosal ulcers, aphthoid ulcers, and pseudo-polyps.[12,13] In the literature, caseous necrosis and the presence of acid-alcohol-resistant bacilli to Ziehl and Nielsen staining allow a definite diagnosis of TB to be established, but are seen in 22% and 26%-36%,

respectively.[1,8,14,15] Therefore, currently available diagnostic confirmation methods have limitations. In our observations, the absence of ascites, gigantocellular granuloma, caseous necrosis during biopsy with absence of acid-fast bacilli at the start misled us and prompted us to erroneously prescribe corticosteroid therapy. This inadequate prescription of corticosteroid therapy led to an explosion of TB symptoms. Demory et al[7] had reported a deceptive case of ITB mimicking CD, leading to inappropriate prescription of corticosteroid therapy, favoring TB explosion with tight stenosis of terminal ileum. Gargouri et al[6] reported a similar situation where corticosteroid therapy exacerbated TB disease. In our observations, corticosteroid therapy led to an explosion and dissemination of TB and allowed us to adjust our initial diagnosis. Therefore, it is imperative to differentiate these two diseases since the immunosuppressant often used in CD can lead to an explosion of TB symptoms or even complications which can be fatal.[1,5-7] Tuberculous ileo-colitis should be ruled out before initiating corticosteroid therapy to avoid possible TB complications.[1,6,7] In our observations, corticosteroid therapy aroused initially inactive pulmonary TB, with secondary appearance of a typical pulmonary radiological image and a positive bascilloscopy. In the literature, this pulmonary involvement can be seen in 9.87%-30% of cases of ITB.[8-10] The response to TB treatment confirms diagnosis if in doubt.[6-8] Some authors have even proposed a therapeutic algorithm for inflammatory ileo-colitis, to make our daily exercise more practical (Figure 5).[3] The management of ITB must be medical and conservative as far as possible, because of the clinical decline of patients (anemia, malnutrition, and immunosuppression).[16] The TB treatment recommended by the majority of guideline in adults is a daily treatment in two phases spread over 2 months of initial quadruple therapy (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol) followed by 4-7 months of dual therapy (Isoniazid and Rifampicin) in maintenance.[1,16-18] The effectiveness of medical treatment is judged on the disappearance of fever, ascites, and weight gain in 4-6 weeks.[16-19] Surgery should be reserved for complicated forms.[20] Our two patients had received a 6-month medical treatment with satisfying outcome and were declared cured at the end of treatment.

4 | CONCLUSION

Intestinal tuberculosis and CD are similar chronic granulomatous diseases, posing a real diagnostic problem. We reported two observations showing an initial diagnostic error in the context of inflammatory ileo-colitis which was almost fatal for our patients due to the spread of TB after corticosteroid therapy. It is essential to differentiate the two pathologies because of the therapeutic implications of CD, which can lead to an explosion of TB symptoms. So far, the diagnosis of ITB remains difficult to achieve in Madagascar. Treatment of ITB should be medical and conservative. Only the complicated forms should resort to surgery.

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CONFLICT OF INTERESTS

None declared.

AUTHORS CONTRIBUTIONS

CIR: contributed to drafting the manuscript. NHR and JAR: contributed to literature search, data collection, and figure preparation. BMR, MR, HDL, SM, ASR, ALRR, and THR: contributed in management of patients in hospital and performed the final manuscript. SHR: contributed to performed the final manuscript. RMR: contributed to study design and performed the final manuscript. All authors read and approved the manuscript.

ETHICAL APPROVAL

The project was approved by the hierarchical heads of University Hospital Joseph Raseta Befelatanana, Antananarivo. Written consent was obtained from the patient for publication of this case report and the accompanying images.

DATA AVAILABILITY STATEMENT

Data available on request from the corresponding author.

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